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VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Re: Comment to Docket Nos. 1976N-0080 and 2000N-1610
Extension for Digoxin Elixir to Obtain Marketing Approval

Dear Sir or Madame:

Lannett Company, Inc. and Liquipharm, Inc., by and through counsel, submit these comments to the above referenced Dockets. These comments address the Notice in the *Federal Register* dated June 29, 2004 (69 FR 38906) extending the date during which unapproved digoxin elixir products can be marketed until at least December 28, 2004. These companies, which made and seek to market Digoxin Elixir Pediatric USP, support the delay, but request that it apply to all companies intending to market the product. The Notice states that the six-month extension "will only apply to manufacturers who have submitted applications to FDA." Lannett has not yet submitted its application.

A. Background

On June 26, 2002, FDA published a final rule revoking 21 C.F.R. §310.500 which established conditions for marketing digoxin products for oral use (tablets and elixir). According to the published final rule, FDA concluded that the regulation establishing batch inspection requirements for digoxin, an older drug, rather than pre-approval requirements, was no longer necessary following its review and approval of GlaxoSmithKline's (GSK's) Lanoxin (digoxin) Tablets in 1997 (NDA 20-405).[1] It has

[1] 67 FR 42992, June 26, 2002.

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generally been FDA's policy to request an application (NDA or ANDA) from all other makers of older grandfathered or DESI (drug efficacy study implementation) products, once one manufacturer obtains approval of its NDA.[2]

In the proposed rule published on November 24, 2000, FDA stated that no unapproved digoxin product could remain on the market as of 30 days following publication of the final rule.[3] A number of objections to that short timeframe were raised by commenters including Roxane, GSK and Jerome Stevens Pharmaceuticals.[4]

FDA generally gives the makers of the unapproved products at least one-year from the date of the first product approval to submit an application before seeking the withdrawal of those products from the marketplace.[5] This policy when applied to guaifensin in 2002, reportedly provoked a hostile response from makers of unapproved products and their trade association, the Branded Pharmaceutical Association. Report language was included in FDA's fiscal 2004 appropriations requesting that FDA consider a monograph system to allow products with a history of safe use to remain on the market.[6] In response to Congressional pressure, and completion of a report requested by appropriators and other interested Members, FDA has reportedly refrained from removing these products from the market.

In its Notice, FDA indicated also that, unlike GSK's Lanoxin Tablets for which a NDA was previously granted, there were no "manufacturers prepared to market digoxin elixir

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2 In Draft Guidance entitled "Marketed Unapproved Drugs-Compliance Policy Guide," Oct. 15, 2003, FDA has stated "Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval. We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective- it also reduces the resources FDA must expend on enforcement." *Id* at 5.

3 65 FR 70539 (Nov 24, 2000).

4 *See* Roxane comments dated Feb. 16, 2001 and JSP comments through its counsel Reed Smith dated December 22, 2000 and Nov. 26, 2001.

5 "When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type." *Id.*

6 "... In an effort to start the dialogue, the [Appropriations] Committee directs FDA to prepare a report for the Committee on Appropriations and the Committee on Health, Education, Labor, and Pensions regarding the feasibility and cost of such a new monograph system for prescription drug products as described above. In the meantime, the Committee believes that enforcement resources regarding pharmaceutical products should be dedicated to activities that are most likely to improve the public health." Committee Rept. 2 of 54-Senate Rpt. 108-107-Agricultural, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2004.

under an approved application."[7] The June 28, 2004 date to obtain marketing approval for the elixir was extended to December 28, 2004 to "assure the continued availability of digoxin elixirs." FDA provided further, however, that "[t]his extension will only apply to manufacturers who have submitted application to FDA and who continue to pursue approval of their applications with due diligence." It was unclear from the language of the Notice whether the applications referred to in this sentence had to be filed prior to the date of the Notice (June 29, 2004), or prior to the date of the extension (December 28, 2004). Finally, FDA left open the possibility that an additional extension would be granted, stating "[w]e will reexamine the need for a continued exercise of enforcement discretion at the end of this 6-month period." The Agency stated that it would "consider whether there is an approved digoxin elixir product on the market and whether the manufacturer is capable of producing sufficient product to meet patient needs."

Currently, there are only two manufacturers of the elixir formulation; Roxane Laboratories which provides approximately 50% of the product and GSK which provides the remaining 50%. Lannett/Liquipharm made the product and intends to resume production shortly. Roxane only recently received FDA approval of its NDA on August 26, 2004 (NDA #21-648). That was the first elixir product to receive product approval. To date, none of the post-NDA Roxane product is on the market for sampling or testing by companies, like Lannett, that intend to conduct bioequivalency studies and submit ANDAs to the Agency. GMP problems with Lannett's contract manufacturer, Biopharma, caused a delay in production and test batches. It caused Lannett to obtain recently another GMP-compliant manufacturing source. The absence of an approved NDA for the elixir formulation and post-NDA product on the market to sample and test for bioequivalency in an ANDA also delayed submission of a completed product approval application.

B. Request. On behalf of Lannett and Liquipharm, the manufacturer and distributor of Digoxin Elixir Pediatric USP, we respectfully request that FDA follow its existing draft compliance policy guidance applicable to unapproved DESI products. This would require FDA to interpret the language of its Notice to refrain from exercising its enforcement discretion to seek the removal of the product from the market unless these companies are unable to prepare and submit a NDA under §505(b)(2) (or an ANDA seeking generic equivalence to Roxane's product) no later than one year following FDA approval of the Roxane NDA , which would be August 26, 2005. In the alternative, FDA should allow companies, like Lannett, to submit their ANDAs before the announced compliance date of December 28, 2004 (assuming that Roxane makes post-NDA product available timely).

C. Rationale. The rationale for this interpretation of the Notice is described below. We would be happy to list additional legal authority and precedent for each of these stated reasons, at your request.

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7 69 FR 38906, June 29, 2004.

1. It is FDA's stated policy in its draft CPG, and in analogous situations (e.g., guaifenesin, levothyroxine, digoxin tablets, etc.) "to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action..."[8] Approval of the first NDA for digoxin elixir occurred on August 26, 2004. ANDA's require access to, and testing of, the post-approval product for bioequivalence (BE) determinations. Assuming that Roxane makes its post-approval formulation available timely,[9] BE testing and preparation of an ANDA for filing with FDA will take at least one-year, or until August 26, 2005.

2. Lannett/Liquipharm has manufactured Digoxin Elixir Pediatric USP since 1984, ceasing production temporarily. No complaints or adverse medical reports have been filed with FDA regarding this pediatric liquid formulation. Eliminating a proven product from competition in the marketplace could disrupt supply and increase price with no demonstrated benefit to public health.

3. Efforts by FDA to revoke §310.500 following the Lanoxin Tablet approval have involved concern over the potency and stability of the tablet formulation, not the liquid elixir.

4. FDA's draft CPG for the marketing of unapproved products in this area is currently under active Agency review. It would be unfair, potentially arbitrary and capricious, and could generate additional Congressional scrutiny, to apply this policy to Lannett, before a final Agency policy has been decided and communicated, while not exercising the Agency's enforcement discretion with respect to the manufacturers of other similarly situated unapproved products.

5. Lannett is diligently working to obtain the data required to prepare an application for FDA approval. Those efforts were delayed by the absence of an approved NDA, listing of a reference product, and the finding of FDA investigators that the contract manufacturing site (for elixir and many products unrelated to Lannett), was out of GMP compliance. These manufacturing responsibilities have been transferred and testing batches are being prepared. Lannett expects to complete BE testing and to prepare a product application for FDA review as soon as Roxane's post-NDA elixir is available, but not later than August 26, 2005.

6. The Notice requires clarification. It states that FDA is "allowing manufacturers to continue to market these products without approved applications until December 28, 2004." It states further that "[FDA] will examine the need for a continued exercise of enforcement discretion at the end of this 6-month period." At the same time, the Notice

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8 *Supra* at note 5.

9 Abbott Labs reportedly took approximately 7 months, or longer, to make its post-NDA Synthroid (levothyroxine sodium) available in the marketplace for BE testing.

states that "This extension will only apply to manufacturers who have submitted applications to FDA and who continue to pursue approval of their applications with due diligence." It does not state expressly that the extension will only apply to manufacturers who have submitted applications to FDA by June 29, 2004, the date of the Notice. Therefore, the Notice can be accurately read to allow submission of the application, and due diligence to pursue approval, anytime during the extension period (up to and including December 28, 2004, unless another extension is granted). The better date in light of FDA's draft CPG, and the recent approval of Roxane's NDA for digoxin elixir, would be August 26, 2005.

7. There is sufficient precedent to permit Lannett to complete its application during this extension period. Abbott Labs was granted multiple extensions to submit a NDA for Synthroid (levothyroxine sodium). Likewise, Jerome Stevens Pharmaceuticals was permitted to continue to market its digoxin tablets despite protests by Bertek and Amide Pharmaceuticals.

8. Finally, it is in the interest of public health to maintain multiple competitors in the marketplace to prevent monopoly control, price increases, supply shortages and limits on consumer choice.

We appreciate your favorable consideration of this matter and your clarification of the Notice requirements, or issuance of a new notice in light of the Roxane approval. We are prepared to work with the Agency to resolve any questions or concerns regarding the status of this product. Please contact Lannett or me with any questions, or if we may be of further assistance.

Best regards.

Sincerely,

Marc J. Scheineson

cc: Mr. Arthur Bedrosian
Ms. Mary E. Catchings